Molecular characteristics of patients with colorectal signet-ring cell carcinoma with different ABO blood groups

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Abstract

Colorectal signet-ring cell carcinoma (SRCC) is a rare subtype of malignant adenocarcinomas. Its biomarker and molecular characteristics remain controversial, and there are no specific therapeutic targets and strategies for clinical treatment. A retrospective study was performed and the extracted data included patients' clinical variables and genomics (either 19-gene or 1021-gene panel NGS). From 2010 to 2021, 64 patients were included. The blood groups of 27 (42.2%), 18 (28.1%), 12 (18.8%), and 7 (10.9%) patients were O, A, B, and AB, respectively. We found that O was a unique blood group which had better prognosis different from non-O blood groups, characterized by a low frequency of KRAS mutations, a high frequency of heterozygous at each HLA class I locus and greater numbers of tumor mutational burden (TMB). Patients with blood group A with high frequency KRAS mutations and patients with blood group B with anemia and metabolic abnormalities had worse OS and needed targeted treatment. The study initially revealed genomic changes in SRCC patients with different blood groups and could advance the understanding and precision treatment of the colorectal SRCC. Blood group O might be a novel target for immunotherapy of colorectal SRCC.

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide. The most common histological subtype of CRC is adenocarcinoma (AC)[1]. Signet-ring cell carcinoma (SRCC) is a rare subtype, accounting for approximately 1–3% and is characterized by the presence of > 50% of tumor cells with prominent intracytoplasmic mucin, typically with displacement of the nucleus[2, 3]. Colorectal SRCC is found associated with younger age and higher tumor grade[4, 5]. It is more often diagnosed in patients with advanced stage disease and usually has poor responses to cytotoxic chemotherapy and radiotherapy compared to patients with conventional adenocarcinoma[6, 7].

Many molecular assessments have suggested a different mechanism of oncogenesis between SRCC and AC. SRCC is characterized by a high rate of MUC2 expression due to the accumulation of mucin in intracytoplasm[8]. SRCC is also associated with a high frequency of MSI-H[9] and mutations that pass through the Ras/MAPK, PI3K/AKT and EMT pathways[10, 11, 12]. Evidence has shown that colorectal SRCC remains a vague entity that resembles AC in some clinicopathological and molecular respects, as well as mucinous adenocarcinoma (MAC). Exploring differences in molecular characteristics is very important for understanding the carcinogenic mechanism of SRCC.

The genomic landscape of colorectal SRCC has been subject to debate. SRCC is still considered an unfavorable and unfamiliar subtype of the disease. Although colorectal SRCC is different from AC in terms of gene expression and histology, SRCC patients currently receive treatments based on the same standard guidelines for classical AC since no clinical guidelines have been developed specifically for this entity. Blood group antigens on the erythrocyte membrane are inherited characteristics, but they are also found in gastrointestinal mucosa. Levels of gut microbiome such as *Faecalibacterium* and *Bacteroides* are associated with ABO genes and blood antigens are used as a preferred source of energy in the

intestine[13]. However, only a few studies have assessed the association between ABO blood groups and CRC risk, and they did not distinguish between bowel cancer subtypes[14, 15]. Thus, it is necessary to recognize the blood groups based on molecular characteristics to guide the individualized treatment of SRCC patients.

In this study, we illustrate for the first time the differences in molecular characteristics of ABO blood groups in SRCC. In addition, we combined both genomic and clinical variables of ABO blood groups to generate a nomogram model with more accurate prediction than clinical risk factors for prognosis.

Materials And Methods

Clinical specimens and study design

This was a single-center, observational prospective study, which was completed in Sun Yat-sen University Cancer Center (SYSUCC). From 2010 to 2021, 64 colorectal SRCC patients were included in the final analysis after excluding patients who lacked off genomic and clinical variables or follow-up information (Table 1). The institutional ethical review boards approved this retrospective analysis of anonymous data, and the requirement for informed consent was waived by the ethics review boards. Clinical characteristics, treatment response, and follow-up results were retrieved from patient medical records and follow-up tracking system. None of the patients had received any anti-tumour therapy before biopsy sampling.

Table 1
Summary of clinical characteristics of colorectal SRCC.

Variables	ABO blood group			
	A	B	O	AB
Age				
< 30	6 (33.33)	2 (16.67)	4 (14.81)	1 (14.29)
30–60	9 (50.00)	7 (58.33)	17 (62.96)	5 (71.43)
≥ 60	3 (16.67)	3 (25.00)	6 (22.22)	1 (14.29)
Gender				
Male	13 (72.22)	4 (33.33)	22 (81.48)	5 (71.43)
Female	5 (27.78)	8 (66.67)	5 (18.52)	2 (28.57)
Smoking history				
Yes	6 (33.33)	3 (25.00)	15 (55.56)	0 (0.00)
No	12 (66.67)	9 (75.00)	12 (44.44)	7 (100.00)
Pathological stage				
	0 (0.00)	0 (0.00)	1 (3.70)	1 (14.29)
	2 (11.11)	1 (8.33)	2 (7.41)	2 (28.57)
	4 (22.22)	1 (8.33)	13 (48.15)	4 (57.14)
	12 (66.67)	10 (83.33)	11 (40.74)	0 (0.00)
Family history				
Yes	5 (27.78)	2 (16.67)	7 (25.93)	0 (0.00)
No	13 (72.22)	10 (83.33)	20 (74.07)	7 (100.00)
Drinking history				
Yes	7 (38.89)	1 (8.33)	6 (22.22)	0 (0.00)
No	11 (61.11)	11 (91.67)	21 (77.78)	7 (100.00)
Adjuvant treatment				
Surgery	14 (77.78)	8 (66.67)	24 (88.89)	5 (71.43)
Radiotherapy	3 (16.67)	2 (16.67)	7 (25.93)	3 (42.86)
Chemotherapy	16 (88.89)	11 (91.67)	26 (96.30)	6 (85.71)

The number in the parentheses is the percentage of this category. DL: distant lymph node.

Variables	ABO blood group			
	A	B	O	AB
Immunotherapy	0 (0.00)	1 (8.33)	2 (7.41)	1 (14.29)
Metastatic site				
Peritoneum	10 (55.56)	7 (58.33)	8 (29.63)	0 (0.00)
Lung	1 (5.56)	1 (8.33)	0 (0.00)	0 (0.00)
Bone	3 (16.67)	1 (8.33)	2 (7.41)	0 (0.00)
Liver	4 (22.22)	0 (0.00)	1 (3.70)	0 (0.00)
Urinary system	1 (5.56)	1 (8.33)	1 (3.70)	0 (0.00)
DL	12 (66.67)	5 (41.67)	4 (14.81)	0 (0.00)
No	6 (33.33)	2 (16.67)	16 (59.26)	7 (100.00)
Total	18	12	27	7

The number in the parentheses is the percentage of this category. DL: distant lymph node.

Pathologic evaluation

Slides from patients whose pathology report documented the presence of signet ring cell histology were obtained and reviewed to confirm the percentage of signet ring cells. Haematoxylin and eosin-stained slides of the tumours were reviewed by two experienced gastrointestinal pathologist. Tumours were classified according to the proportion of signet ring cells, with ≥ 50% defining SRCC.

Clinical characteristics

Demographic and clinical information, including age, gender, ABO blood group, metastasis site, date of last follow-up and date of death, were collected from a review of patient medical records (Table 1, Table S1). Staging was performed using the American Joint Committee on Cancer/Union for International Cancer Control TMN staging system (version 8, 2017). Overall survival (OS) was defined as the interval between the date of diagnosis of metastatic disease and the date of death from any cause. Patients alive at the time of analysis were censored at their last known follow-up date.

NGS and alteration identification

Primary SRCC samples from 10 patients were sequenced using a set of predesigned and prevalidated assays (v 1.0; Sequenom Inc., San Diego, CA, USA), which were used for identification of 238 candidate mutations harboring 19 cancer-associated genes: ABL1, AKT1, AKT2, BRAF, CDK, EGFR, ERBB2, FGFR1, FGFR3, FLT3, HRAS, JAK2, KIT, KRAS, MET, NRAS, PDGFRA, PIK3CA, and RET (Table S2). The mutations of each oncogene are shown in Supplemental Table S1. The assay protocol is shown in Table S3. Matrix

chips were analyzed with MassARRAY Typer software (v4.0; Sequenom Inc.) with a predefined cutoff mutation frequency of 1%[16].

Primary SRCC cancers from 11 patients were sequenced using a customized panel of 1021 cancer-related genes in the Department of Molecular Diagnostics. These 1021 sequenced genes are listed in Table S4. Detected somatic variations included single nucleotide variations, small insertions and deletions (InDels), copy number variations, and gene fusions. Detailed information on sample processing, DNA extraction, library construction, target capture, NGS, and data analysis is described in Table S5-S6. We defined TMB as the number of somatic mutations and indels per megabyte bases in coding regions detected in tumor tissues.

Statistical analysis

GraphPad Prism software, version 8, was used for data analysis. The Kaplan-Meier method was used to estimate survival distributions, the differences in OS were analyzed with the log-rank statistic and hazard ratios (HRs) were calculated using a univariate Cox regression analysis. Covariates included ABO blood group, gender, age (> 45 years vs ≤ 45 years), T stage (T3–4 vs T1–2), N stage (N2–3 vs N0–1), M stage (M1 vs M0), serum TBA (> 9.8 vs ≤ 9.8 μmol/L), PT (> 11.9 vs ≤ 11.9 s), CHO (> 4.64 vs ≤ 4.64 mmol/L), INR (> 1.04 vs ≤ 1.04), HDL-C (> 1.23 vs ≤ 1.23 mmol/L), ApoA1 (> 0.96 vs ≤ 0.96 g/L) and peritoneal metastatic (yes vs no) (Table S7-S8). We also did a multivariate Cox regression analysis of colorectal SRCC using backward selection to test the independent significance of different factors; the *P* value threshold was 0.1 ($P > 0.1$) for removing non-significant variables from the analysis, and marginally significant variables ($0.05 < P < 0.1$) remained in the final Cox model. All statistical tests were two-sided, and *P* values of less than 0.05 were deemed significant. Clinical follow-up was completed by March 2022.

Results

Patient characteristics and metastatic patterns

We included in our analysis 64 pretreatment, colorectal SRCC specimens that were obtained from Sun Yat-sen University Cancer Center. The clinicopathological characteristics of this cohort are summarized in Table 1 and Fig. 1. Of the 64 included patients, 44 were males (68.75%) and 20 were females (31.25%), and the ratio of males to females was 2.2. The median age at diagnosis was 44.5 years (range, 20 to 91), and forty-five percent of the patients(n = 29) were younger than 40 years at the time of diagnosis. A family history of cancer was reported in 21.88% of patients, while a smoking history was reported in 34.38%. Overall, 27 (42.2%), 18 (28.1%), 12 (18.8%), and 7 (10.9%) patients had blood groups O, A, B, and AB, respectively.

There was a statistically significant finding in the family history of cancer distribution, where 50% of those with blood group O had a family history of cancer compared to 35.7% and 14.3% of those with blood group A and B (Fig. 1A). Thirty-three percent of the patients (6/18) with blood group A and fifteen

percent of the patients (4/27) with blood group O were younger than 30 years at the time of diagnosis (Fig. 1B). SRCC was significantly more prevalent in females with blood group B, and in males with the other three blood groups (Fig. 1C). The proportions of patients with blood group O classified as having American Joint Committee on Cancer (AJCC) stage I, II, III, and IV diseases were 3.70%, 7.41%, 48.15%, and 40.74%. Patients with A and B blood groups were more likely to belong to stage IV (Fig. 1D). Patients with blood group B had the highest rate of distant metastases and type AB had the lowest (Fig. 1E).

Patients with blood group B had significantly worse OS ($P = 0.06$) and PFS ($P < 0.05$) than patients with blood group O (Fig. 2A-D), the prognosis of patients with blood groups A and AB was not significantly different from that of blood group O (Fig. S1A-B). Six metastatic sites (peritoneum, bone, liver, lung, urinary System and distant lymph node) were identified in the cohort. Among these metastatic sites, the lung was the least common metastatic site in colorectal SRCC, accounting for 6.1% (2/33) of metastatic sites, respectively. Peritoneum was the most common metastatic sites (72.7%; 8/11) in patients with blood group O. And distant lymph nodes were the most common metastatic sites (100%; 12/12) in patients with blood group A (Fig. 2E). In colorectal SRCC, patients with peritoneum metastasis had a worse prognosis than patients without metastasis ($P < 0.01$) (Fig. 2F). Lung metastasis also have a distal effect on prognosis ($P < 0.0001$), and there was no significant difference in the prognostic impact of metastasis at other sites (Fig. S1C-H). In addition, anemia did not affect the prognosis of SRCC (Fig. 2H).

Clinical variables

The level of arterial PCO2 (PaCO2) in patients with blood group B was lower than patients with blood group A and O ($P < 0.05$), the phenomenon suggested that the patients were in abnormal metabolic states (Fig. 3A). The red blood cell-related factors HGB, MCHC, MCH were at the lowest levels in blood group B (Fig. 3B-D). Univariate analysis by Kaplan–Meier survival analysis and log-rank test was performed using several factors, including age, gender, histological grade, family history and clinical variables. Factors found to be significantly associated with worse OS were blood groups (A, B), serum TBA (> 9.8 μmol/L), PT (> 11.9 s), CHO (> 4.64 mmol/L), INR (> 1.04), HDL-C (> 1.23 mmol/L), ApoA1 (> 0.96 g/L) and peritoneal metastasis (Fig. 3E-F). Multivariate logistic regression analysis indicated that peritoneal metastasis and PT were independently associated with survival (Peritoneal metastasis, odds ratio = 2.639, 95% confidence interval: 1.046–6.658, $P = 0.040$; PT, odds ratio = 1.396, 95% confidence interval: 1.037–1.878, $P = 0.028$; Table 2).

Table 2
Univariate and multivariate analyses of OS in patients with colorectal SRCC.

Variables	Univariate		Multivariate	
	OS HR (95% CI)	*P* value	OS HR (95% CI)	*P* value
ABO blood group				
O	Reference			
A	2.649(0.838, 8.371)	0.097		
B	3.023(0.919, 9.943)	0.069		
AB	1.920(0.453, 8.131)	0.376		
Gender				
Male	Reference			
Female	0.939(0.360, 2.450)	0.898		
M1	3.280(1.262, 8.522)	0.015		
N2	5.040(1.127, 22.537)	0.034		
Stage 3	7.980(1.037, 61.423)	0.046		
Peritoneal metastasis	3.330(1.372, 8.083)	0.008	2.639(1.046, 6.658)	0.040
Bone metastasis	2.748(0.591, 12.771)	0.197		
Liver metastasis	2.713(0.784, 9.390)	0.115		
Lung metastasis	15.365(2.794, 84.501)	0.002		
DL metastasis	1.904(0.805, 4.504)	0.143		
PT	1.542(1.161, 2.049)	0.003	1.396(1.037, 1.878)	0.028
INR	108.816(5.295, 2236.403)	0.002		
TBA	1.036(1.014, 1.059)	0.001		
HDL-C	5.148(1.477, 17.950)	0.010		
ApoA1	6.943(1.368, 35.243)	0.019		
CHO	1.572(1.084, 2.279)	0.017		
LDL-C	1.481(0.997, 2.199)	0.052		
CI	0.818(0.708, 0.944)	0.006		
No Surgery	0.630(0.242, 1.644)	0.345		

HR: hazard ratio; CI: confidence interval.

Variables	Univariate		Multivariate	
	OS HR (95% CI)	*P* value	OS HR (95% CI)	*P* value
No Immunotherapy	0.373(0.049, 2.832)	0.340		
No Radiation	0.799(0.305, 2.093)	0.648		
No Chemotherapy	1.431(0.191, 10.731)	0.728		
No Transfusion	0.779(0.180, 3.370)	0.738		
HR: hazard ratio; CI: confidence interval.				

Molecular characteristics

11 cases were tested with the 1021-gene panel while 10 cases were tested with the 19-gene panel. Genetic mutations were detected in 66.7% of the SRCC tumors (14/21) and details relating to gene mutation frequencies in 4 blood groups were shown in Fig. 4. Compared with blood group A and B, O was commonly found with KRAS wild-type (WT). 3 cases (14.3%, with microsatellite instability-high) were considered as hypermutated (Fig. 4A, C). The most common alteration in SRCC was point mutation in TP53 (4 missense mutation and 1 splice site mutation, 5/11, 45%) and the next common alterations were heterozygous mutations in HLA-I (3/11, 36%) and multiple mutations in ATM (3/11, 36%). By comparing mutated genes in different cancer signaling pathways, we found that the frequency of mutations in p53 (e.g., TP53) and TGF-β (e.g., SMAD4) pathways was higher, however the mutation burden in WNT, MAPK, and PI3K pathways were dramatically lower in colorectal SRCC (Fig. 4A-B). TP53, ATM and HLA-I mutations in patients with blood group O were more prevalent compared to their mutations in patients with other blood groups. Patients with blood group O had a higher tumor mutation burden (TMB) than other groups (Fig. 4D).

Discussion

Colorectal SRCC has been considered a distinct histological subtype of CRC based on clinicopathological features, genetic features and clinical outcomes. However, there are still some problems. First of all, SRCC is a rare subtype of colorectal cancer, but previous SRCC studies are focused only few cancer gene mutations and expressions or case reports. Some population-based studies have noted that SRCC commonly presents at a young age[17]. However, it remains controversial, as Lanjuan Li et al. reported a much older age at diagnosis, of 64.5 years old[18]. None of the above studies analyzed the differences in the distribution of different ABO blood groups, and our study revealed for the first time that blood group A was highly prevalent in younger people, while the other three blood groups were significantly more prevalent in older groups. A prospective study of a cohort of middle-aged or older Chinese men demonstrated a lower risk of all cancer for blood group B, as well as lower risk for gastrointestinal cancers including colorectal cancer[19]. However, the study did not analyze the relationship between different CRC subtypes and blood groups. Our study found that SRCC patients with blood group B were

often diagnosed at an advanced stage, had rapid disease progression and a far worse PFS than people with blood group O. In addition, due to abnormal metabolism, PaCO2 levels were generally low in patients with blood group B, and the degree of anemia was more severe in patients with blood group B than other groups.

Secondly, the ABO blood group antigens could influence tumorigenesis by changing intercellular adhesion, membrane signaling and immune surveillance[20]. Some studies have reported the lack of association between ABO blood groups and CRC, Khalili et al found no significant association between blood group B and the overall risk of colon cancer[21]. However, Urun et al reported that ABO/Rh blood groups were significantly associated with CRC, and there was no relationship between KRAS mutation and ABO blood groups[22]. None of the previous studies analyzed the relationship between different subtypes of CRC and ABO blood groups. Since the clinicopathological features and genomic changes of different subtypes of CRC are completely different, previous studies on the relationship between ABO blood group and CRC are not sufficiently illustrative. Our study focused on the rare subtype of SRCC and revealed for the first time that blood group A and blood group B were independent factors contributing to the poor prognosis of SRCC by univariate and multivariate Cox proportional hazards models.

Lastly, due to the rarity of the subtype, genomic alteration data in SRCC are scarce. However, SRCC, as a subtype that is not sufficiently sensitive to radiotherapy[23] and has extremely rapid progression and poor prognosis, urgently needs to be studied in depth. Colorectal SRCC is significantly associated with more peritoneal metastasis, lower KRAS or BRAF mutation rate[24], lower E-cadherin expression[25, 26] and more MUC2 expression[27] than AC, but some studies have shown that BRAF mutation must be closely associated with the presence of malignant signet ring cells regardless of their percentages[28]. Although previous studies show that SRCC and AC have different genetic features, it is still difficult to fully understand SRCC due to lack of multi-omics analyses. No clinical guidelines has been developed specifically for this entity, it is necessary to reveal the molecular features for guiding the prognosis and precise treatment of colorectal SRCC patients. Here we comprehensively analyzed clinical and genomic data of 64 cases of SRCC from our center. Our results showed that the high frequency mutations of blood group O were TP53, ATM, HLA-I while those of blood group A were KRAS and ALK. KRAS mutations influence multiple pathways including the RAS-RAF-MEK-ERK and PI3K-AKT-mTOR pathways, which regulate cell cycle, promote cell growth and suppress apoptosis, and play a key role in carcinogenesis by inducing an array of inflammatory cytokines, chemokines and accentuates tumorigenesis and invasiveness[29]. The impact of KRAS mutations might explain the prognosis of patients with blood group A. Patients with blood group O had a higher TMB than others. HLA-I has been extensively used as a biomarker for immunotherapy, and its heterozygous has been associated with disease progression[30]. Immunotherapy benefits some patients with metastatic cancers, However, so far, only 20%-40% of tumor patients have responded to immunotherapy[31, 32]. PD-1 antibody gains regulatory approval for the treatment of dMMR/MSI-H metastatic CRC in 2017. In addition, patients with high TMB have higher response rate and longer survival time on PD-1 inhibitor therapy across multiple cancer types[33]. HLA-I heterozygous mutation is associated with TMB and the HLA-corrected TMB can help to identify patients

who do not respond to immune checkpoint inhibitors (ICIs) despite having a high TMB[34]. Previous reports have shown that HLA-I homozygosity and low mutation burden were strongly associated with decreased survival compared to patients who were heterozygous at each class I locus and the combined effect of HLA class I heterozygosity and TMB on improved survival was greater compared with TMB alone[30, 35]. They identified three alleles, as possessing a structural bridge in the peptide-binding groove (Arg62, Ile66, and Leu163), and the specific structural feature might modulate the effective T cell recognition of neoepitopes presented on HLA. Our results also showed that SRCC patients who were heterozygous at each HLA class I locus had better prognosis and they belonged to blood group O. Moreover, patient O10 with HLA-I heterozygous mutation, survived more than 10 years after receiving the left hemicolectomy, appropriate chemotherapy and 12 doses of immunotherapy (Sintilimab Injection). Our study revealed for the first time the differences in clinical features and molecular profiles of SRCC in different ABO blood groups. We performed exon sequencing in 21 cases of SRCC and found that patients with blood group O had the potential to benefit from immunotherapy, and that people with A and B blood groups were at high risk of poor prognosis of SRCC. Due to the limitation of the sample size of this project, more studies are needed to prove the findings, and we expect more investigators to focus on this aggressive histological type.

In conclusion, our study revealed different clinical features and molecular profiles of SRCC in different ABO blood groups. Patients with blood group A with high frequency KRAS mutations and patients with blood group B with anemia and metabolic abnormalities had worse OS and needed targeted treatment. Furthermore, some clinical variables such as PT and INR were put forward to predict prognosis of SRCC. Finally, we also delineated SRCC patients with blood group O were heterozygous at each HLA class I locus and had better prognosis. Blood group O might be a novel target for immunotherapy of colorectal SRCC.

Statements And Declarations

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Competing Interests

None.

AUTHORS CONTRIBUTION

All authors contributed to the study conception and design. W-NZ and W-QL designed the study. W-NZ, W-JL, YZ and M-JL collected the data. M-JZ, M-LK, X-ZW, R-H, M-YW, Y-NL, and QC analysed and interpreted the data. W-NZ and W-JL wrote the manuscript. YZ, M-JZ, and M-LK revised the manuscript. W-NZ and W-

JL did the statistical analysis. All authors were involved in writing the paper and had final approval of the submitted and published versions.

Data Availability

The key raw data have been uploaded onto the Research Data Deposit public platform (RDD), with the approval RDD number of RDDA2022938685.

Ethics approval

The institutional ethical review boards approved this retrospective analysis of anonymous data, and the requirement for informed consent was waived by the ethics review boards (2022-05-30/B2022-353-01).

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Figures

Figure 1

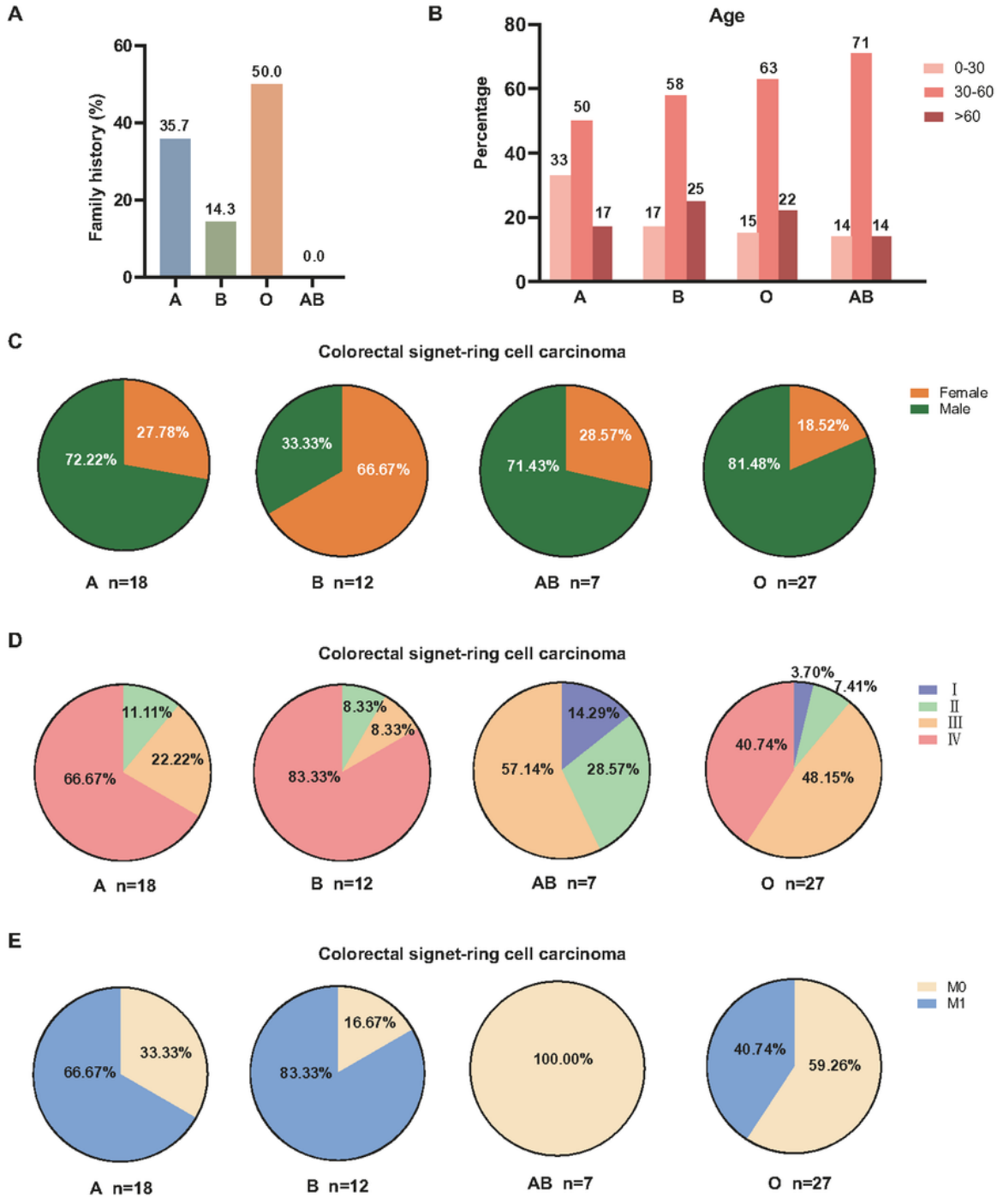

Figure 1

Summarized characteristics of 64 colorectal SRCC patients with different ABO blood groups. A. Family history of SRCC patients with different ABO blood groups. B. Age distribution of SRCC patients with different ABO blood groups. C. Gender distribution of SRCC patients with different ABO blood groups. D. Pathology stage distribution of SRCC patients with different ABO blood groups. E. Metastases distribution of SRCC patients with different ABO blood groups.

Figure 2

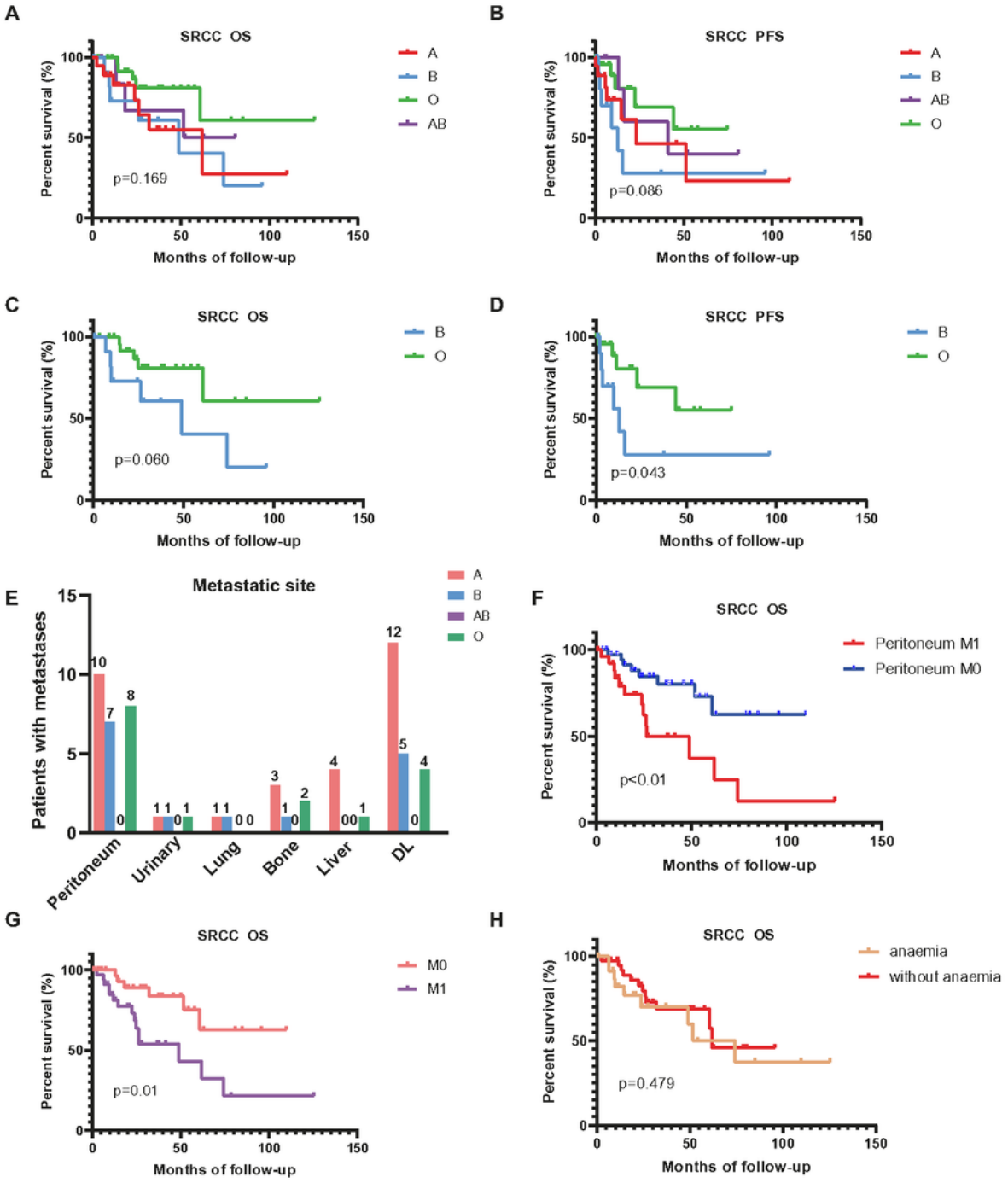

Figure 2

Kaplan–Meier analysis of OS and PFS in colorectal SRCC patients. A. Kaplan–Meier analysis of OS in patients with different blood groups (log-rank *P*=0.169). B. Kaplan–Meier analysis of PFS in patients with different blood groups (log-rank *P*=0.086). C. Kaplan–Meier analysis of OS in patients with blood group B and O (log-rank *P*=0.060). D. Kaplan–Meier analysis of PFS in patients with blood group B and O (log-rank *P*=0.043). E. Distribution of distant metastatic sites in colorectal SRCC. F. Kaplan–Meier

analysis of OS in patients with and without peritoneum metastasis (log-rank *P*<0.01). G. Kaplan–Meier analysis of OS in patients with and without metastasis (log-rank *P*=0.01). H. Kaplan–Meier analysis of OS in patients with and without anaemia (log-rank *P*=0.479).

Figure 3

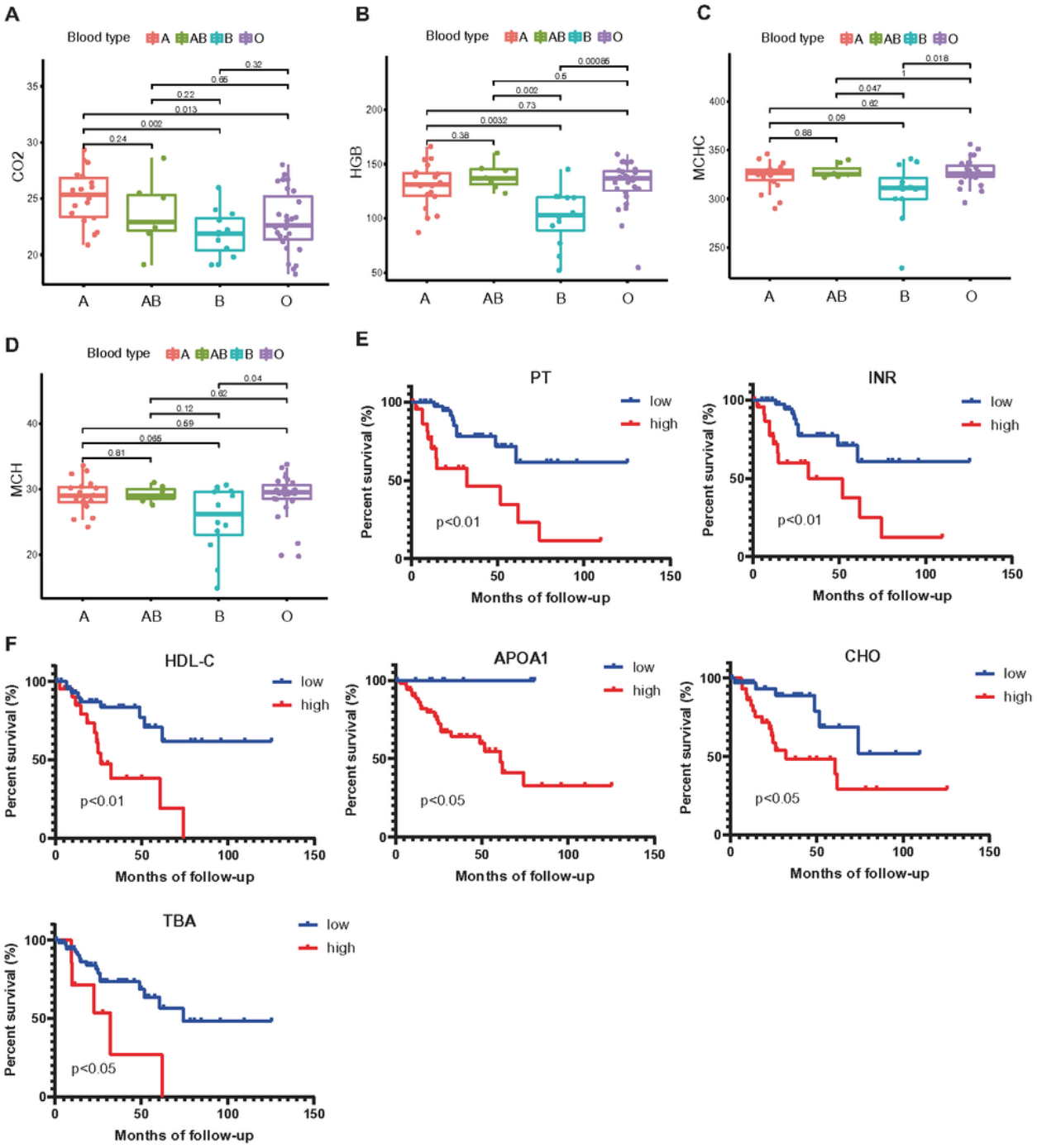

Figure 3

Clinical variables of colorectal SRCC patients with different blood groups. A. Serum CO2 levels of four blood groups. B. HGB levels of four blood groups. C. MCHC levels of four blood groups. D. MCH levels of four blood groups. E. Kaplan–Meier analysis of OS in patients with different groups (Coagulation-related clinical variables, log-rank *P*<0.01). F. Kaplan–Meier analysis of OS in patients with different groups (four clinical variables, log-rank *P*<0.05).

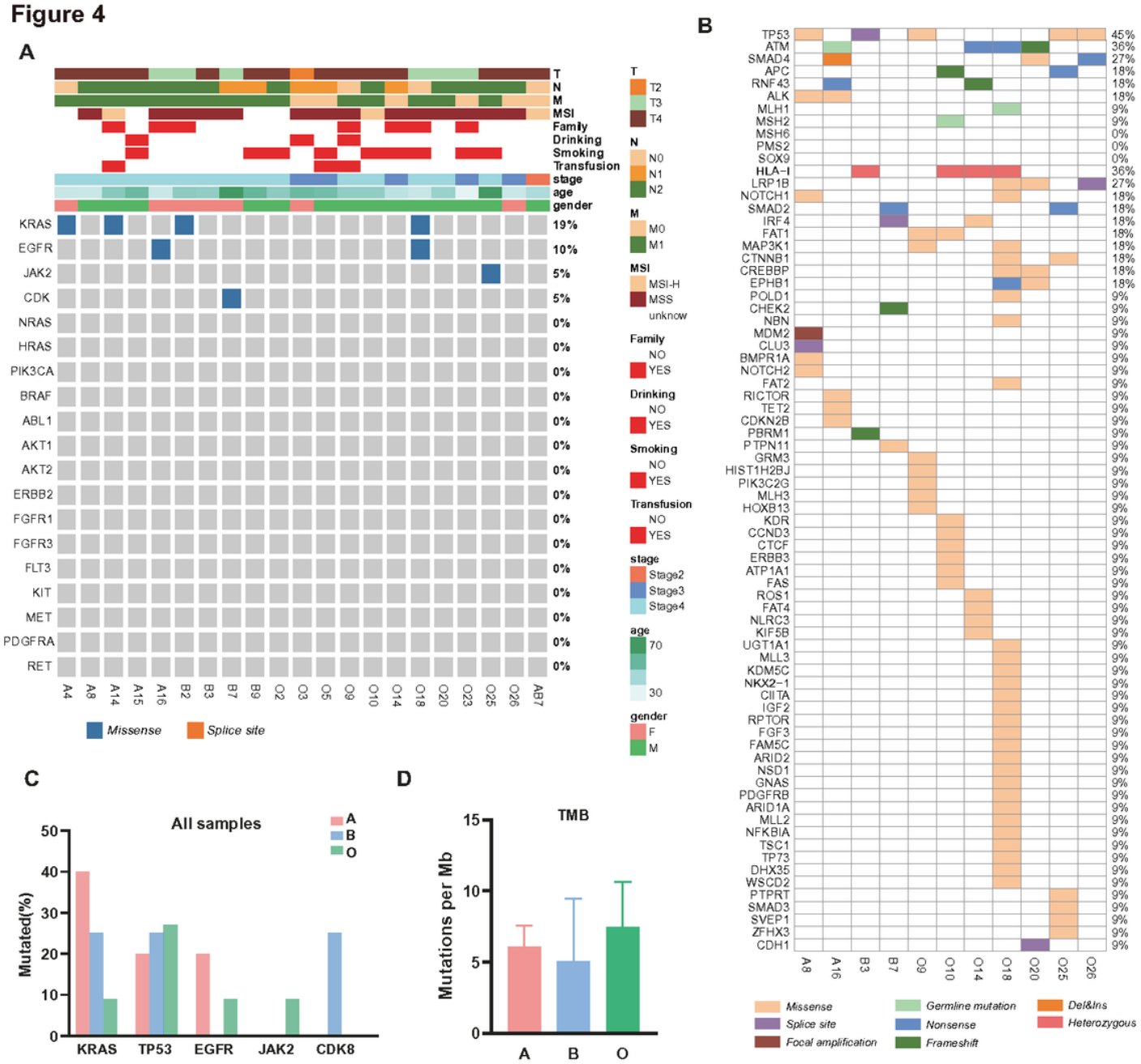

Figure 4

The molecular features of colorectal SRCC patients with different ABO blood groups. A. Gene mapping of four blood groups in colorectal SRCC (19-gene panel). B. Gene mapping of four blood groups in colorectal

SRCC (1021-gene panel). C. Comparison of mutation rates of cancer drivers of three blood groups in colorectal SRCC. D. Tumor Mutation Burden of three blood groups in colorectal SRCC.

Supplementary Files

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